

**BLA:** *STN 103471*  
*Betaseron<sup>®</sup> (Interferon **b**-1b) for the treatment of secondary*  
*progressive multiple sclerosis.*  
Submission dated June 29, 1998.  
*Chiron Corp.*

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**Date:** *March 11, 2003*  
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The clinical and statistical issues related to the review of this BLA have been discussed with the staff from the Division of Clinical Trial Design and Analysis. This reviewer has analyzed the electronic data submitted by the sponsor. Results of our analyses are consistent with those given in the clinical report submitted by the sponsor. This review will summarize the observed results on the primary and key secondary efficacy endpoints. A more detailed description of the safety and efficacy results, including some results of exploratory analyses, are given in the Medical Officer's Clinical Review.

## **Study Design**

This study was a double-blind, multicenter, placebo-controlled trial of two dosing regimens of Betaseron given to patients in US and Canada with secondary progressive multiple sclerosis (SPMS). A total of 939 patients with well-documented SPMS were enrolled at 35 sites in the US and Canada.

Patients were equally randomized to receive either placebo, Betaseron 8MIU, or Betaseron 5 MIU/m<sup>2</sup> of body surface area in a 1:1:1 ratio. In order to match the different Betaseron treatment regimens, the placebo group was further randomized so that 50% of patients received a fixed 1.0 mL of placebo solution and 50% received a fraction of 1.0 mL of placebo solution based on the individual patient's body surface area. All patients escalated their doses in weekly increments during the first 3 weeks of treatment and received ibuprofen 1200 mg/day during the first 7 weeks of treatment. This

treatment initiation strategy was designed to reduce the frequency and severity of flu-like symptoms and thus minimize the potential for patient unblinding based on side effects.

The total treatment duration was 156 weeks.

### **Primary Efficacy Endpoint: Time to confirmed neurological deterioration**

The primary efficacy variable (time to confirmed neurological deterioration) was defined as one point or greater increase from baseline EDSS score that must be sustained for at least six months as documented by confirmatory visits (0.5-point increase for patients with a baseline EDSS of 6 or 6.5). Time to such confirmed progression was defined as the number of days from start of dosing to the onset of the first increase of at least 1.0 EDSS point over baseline (at least 0.5 point increase for those patients with a baseline EDSS of 6 or 6.5). This EDSS increase from baseline had to be maintained and confirmed at two subsequent consecutive 12-week visits to be considered valid. Progression that occurred at the next-to-last available visit for a patient needed to be confirmed by only one repeat examination, at least 70 days later, and this confirmation must have taken place by the patient's last study visit. All missing EDSS scores were maintained as missing during the analyses. An initial progression followed by a missing EDSS score required confirmation by the next two 12-week visit score.

The Kaplan-Meier product-limit method was used to describe the distribution of time to progression. The logrank test was used to test for the difference between the treatment groups. Patients lost to follow-up were censored at the time of their loss.

### **Secondary Efficacy Endpoints**

The following 5 secondary endpoints were specified in the protocol:

1. Change in mean EDSS score from baseline to endpoint
2. Annual relapse rate
3. Absolute change in annual T2 lesion area from baseline to endpoint
4. Annual newly active lesion rate
5. Change in composite neuropsychologic score from baseline to endpoint

The absolute change in annual T2 lesion was analyzed by using an analysis of covariance (ANCOVA) based on ranked data and adjusted for the ranks of the baseline lesion burden. The main effects were treatment, study site, and treatment-by-study site interaction.

All other endpoints were to be analyzed by the method of ANOVA with main effects as treatment, study site, and treatment-by-study site interactions.

## Sample Size

The study size of 900 patients was estimated with the following assumptions:

- 50% of the patients would experience a confirmed progression by the end of the 3-year study.
- A clinically relevant treatment effect was a relative 30% reduction as compared to placebo (an absolute reduction of 15%).
- An alpha level of 0.05.
- A power of 95%.
- A dropout rate of 10%.

## Interim Analysis

An Independent Monitoring Board (IMB) was used to review safety and efficacy data at every six months. There were seven interim analyses, approximately 6 months apart, prior to the final analysis. The method of Fleming, Harrington, and O'Brien was used for alpha spending during the interim analyses. At a scheduled meeting of the IMB in August of 1999, the committee recommended early termination of the study after reviewing the available data related to the primary outcome measure, available secondary outcome measures, and safety data.

A two-stage testing procedure was used for the hypothesis testing. In the first stage, the two Betaseron doses were combined for a test against placebo at the required alpha-level for the analysis. If the null hypothesis of no difference between Betaseron and placebo was rejected during the first stage, the two doses of Betaseron were individually compared to placebo at the same alpha-level used in the first stage.

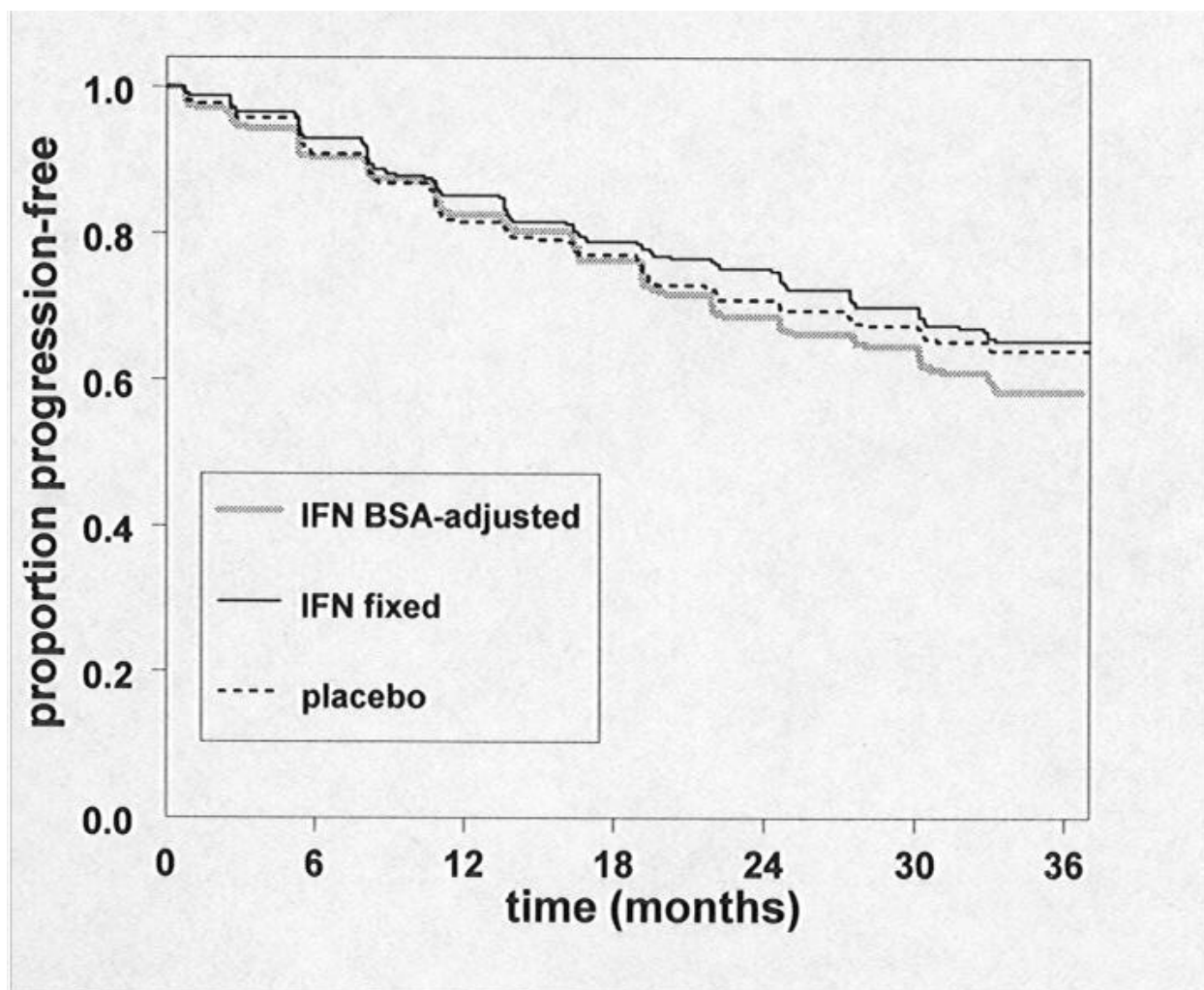
## RESULTS

### I. Primary Efficacy Endpoint: Time to confirmed neurological deterioration

A Kaplan-Meier curve of the time to confirmed neurological deterioration based on EDSS score is given in figure 1. There were no significant differences between all *Betaseron* (i.e., *Betaseron* groups combined) and placebo ( $p=0.71$ ), *Betaseron* 8MIU and placebo ( $p=0.61$ ), and *Betaseron* 5 MIU/m<sup>2</sup> and placebo ( $p=0.26$ ).

A Cox regression analysis using center, baseline EDSS, and duration of MS as covariates also did not show any significant difference.

Figure 1. Kaplan-Meier survival curve of the primary endpoint: Time to confirmed neurological deterioration.



## II. Secondary Efficacy Endpoints

The efficacy results for the prospectively defined secondary efficacy endpoints are given in Table 1.

### 1. Change in mean EDSS score from baseline to endpoint

The observed changes in mean scores were 0.62, 0.53, and 0.72 for placebo, 8 MIU, and 5 MIU/m<sup>2</sup> groups, respectively. The ANOVA p-values were not statistically significant (Table 1).

### 2. Annual relapse rate

The observed mean annual relapse rates for placebo, 8 MIU, and 5 MIU/m<sup>2</sup> groups were 0.28, 0.16, and 0.20, respectively. Comparisons between all Betaseron versus placebo and 8 MIU versus placebo showed p-values less than 0.05 (Table 1).

### 3. Absolute change in annual T2 lesion area from baseline to endpoint

The data from this trial showed a highly significant effect of Betaseron on this endpoint (all p-values  $\leq 0.0001$ ). The mean absolute change of total MRI lesion area was 637, 107, and 134 mm<sup>2</sup> for the placebo, 8 MIU, and 5 MIU/m<sup>2</sup> groups, respectively (Table 1).

### 4. Annual newly active lesion rate

The newly active lesion rates were evaluated using MRI data from a subgroup of 163 patients. These patients underwent MRI scans every 4 weeks throughout the study. The annualized newly active lesion rate was calculated by computing the cumulative number of newly active lesions and dividing by the number of scans used in the cumulative computation.

The observed mean annual active lesion rates were 18.7, 6.4, and 4.5 in the placebo, 8 MIU, and 5 MIU/m<sup>2</sup> groups, respectively. The p-values were 0.0001 for all Betaseron versus placebo, 0.003 for 8 MIU versus placebo, and 0.0001 for 5 MIU/m<sup>2</sup> versus placebo (Table 1).

### 5. Change in composite neuropsychologic score from baseline to endpoint

The mean change from baseline to endpoint for the placebo, 8 MIU, and 5 MIU/m<sup>2</sup> groups was –0.32, –0.28, and –0.30, respectively, from baseline means of –0.83, –0.80, and –0.81. There were no significant differences between the treatment groups (Table 1).

Table 1. Summary of the secondary efficacy endpoints.

Secondary Endpoints	Placebo	Betaseron 8 MIU	Betaseron 5 MIU/m <sup>2</sup>	P-value
Change in mean EDSS score from baseline to endpoint	0.62	0.53	0.72	0.629 <sup>a</sup> 0.634 <sup>b</sup> 0.214 <sup>c</sup>
Annual relapse rate	0.28	0.16	0.20	0.014 <sup>a</sup> 0.009 <sup>b</sup> 0.109 <sup>c</sup>
Absolute change in annual T2 lesion area (mm <sup>2</sup> ) from baseline to endpoint	637	107	134	<0.0001 <sup>a</sup> 0.0001 <sup>b</sup> 0.0001 <sup>c</sup>
Annual newly active lesion rate*	18.7	6.4	4.5	0.0001 <sup>a</sup> 0.003 <sup>b</sup> 0.0001 <sup>c</sup>
Change in composite neuropsychologic score from baseline to endpoint	-0.32	-0.28	-0.30	0.475 <sup>a</sup> 0.420 <sup>b</sup> 0.721 <sup>c</sup>

\* Based on frequent MRI substudy patients (n=163)

a All Betaseron versus placebo

b 8 MIU versus placebo

c 5 MIU/m<sup>2</sup> versus placebo

## Conclusions

1. The results of this clinical trial show that there is no effect of Betaseron (8 MIU or 5 MIU/m<sup>2</sup>) on disease progression in SPMS patients as measured by time to progressive neurological impairment based on EDSS score (the primary endpoint). Furthermore, there is no significant effect of Betaseron on two secondary endpoints: change in mean EDSS score from baseline to endpoint and change in composite neuropsychologic score from baseline to endpoint.
2. These data do show some effect of Betaseron treatment on the MRI endpoints: absolute change in annual T2 lesion area from baseline to endpoint and annual newly active lesion rate.
3. Betaseron treatment was also associated with approximately 33% reduction in the annual relapse rate.